Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q4W 350 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2 to 5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Carotid artery stenosis, Nephrolithiasis

Subject [redacted] was a 71-year-old white man participating in Study 20110110 who developed carotid artery stenosis (reported term: carotid stenosis right side) and nephrolithiasis (reported term: kidney stone). The subject's medical history included hypercholesterolemia, hypertension, hyperlipidemia, myocardial ischemia, coronary artery bypass graft, aortic valve replacement, transient ischemic attack with right sided symptoms, and percutaneous transluminal coronary angioplasty. Concomitant medications included amlodipine, clopidogrel, metoprolol, glyceryl trinitrate, and cilostazol. According to the investigator, the subject did not receive any previous treatment for hypercholesterolemia since ezetimibe was stopped more than 6 months before initiation of study.

The subject was in the parent study from 10 November one year ago* to 31 January same year* and received the last dose of evolocumab in the parent study on 03 January same year*. The subject received the first dose of evolocumab in Study 20110110 on 31 January [redacted]. Baseline calculated low-density lipoprotein cholesterol was 221.5 mg/dL on 10 November one year ago* (parent study).

On 30 October same year*, the subject was hospitalized for planned surgery due to bilateral carotid artery stenosis (80% to 90% stenosis of left internal carotid and 70% to 80 % stenosis of right internal carotid). The next day, on 31 October same year*, the subject underwent a thromboendarterectomy for stenosis of the carotid artery (left internal) and a Dacron patch was used. The surgery went well and a follow up visit was planned in approximately 1 month. The investigator stated that the final outcome for the event of carotid artery stenosis was not resolved, as surgery of the left carotid was done on 31 October same year*; however, surgery for the right side had not been done and had not yet been planned. The subject was discharged from the hospital on 02 November same year*. Evolocumab was continued.

Approximately 1 year and 4 months after the first dose of evolocumab in Study 20110110, on 18 May one year after*, the subject was hospitalized due to a kidney stone. Laboratory test results showed hemoglobin of 134 g/L and creatinine of 130 µmol/L. Unspecified examinations revealed a left side distal ureteral stone that was 1.5 cm in size, with dilatation over the ureter.

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On 20 May one year after*, the subject underwent an endoluminal ureterolithotomy with laser and double J ureteral stent insertion. Post-operative progress was good, the catheter was extracted and the subject micturated by himself. On the same date, creatinine was 100 µmol/L. The event of nephrolithiasis was reported to have resolved on 20 May one year after*, and the subject was discharged from hospital. The investigator confirmed that there were no etiological risk factors for the event.

The subject's last dose of evolocumab prior to the events of transient ischaemic attack and carotid artery stenosis was on 10 October same year*, and the last dose of evolocumab prior to the event of nephrolithiasis was on 23 April one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and the last dose of evolocumab prior to the cutoff date was on [redacted]. The investigator reported that there was no reasonable possibility that the events of carotid artery stenosis and nephrolithiasis were related to evolocumab.

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Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q4W 350 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2 to 5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Angina pectoris

Subject [redacted] was a 50-year-old white man participating in Study 20110110 who developed angina pectoris (reported term: low threshold angina/cardiac). The subject's medical history included hypercholesterolemia, low-threshold angina, coronary artery disease, non ST segment elevation myocardial infarction, bypass surgery, hypertension, hyperlipidemia, ex-smoker, gastroesophageal reflux disease, allergic rhinitis, facial reconstructive surgery, Vitamin D deficiency, herpes zoster virus, erectile dysfunction, occasional alcohol use, previous tobacco use (quit in four years ago*), drug hypersensitivity to penicillin (rash), atorvastatin and rosuvastatin (muscle weakness for both), and a family history of premature heart disease. Concomitant medications included acetylsalicylic acid, esomeprazole, valaciclovir, glyceryl trinitrate, vardenafil, Vitamin D_3, metoprolol, multivitamins, and amlodipine. The investigator stated that the subject did not receive any previous treatment for hypercholesterolemia.

The subject was in the parent study from 26 September same year* to 22 December same year* and received the last dose of evolocumab in the parent study on 21 November same year*. The subject received the first dose of evolocumab in Study 20110110 on 22 December [redacted].

In April one year after*, the subject had a catheterization that showed adequate graft function, but there was a second diagonal vessel that showed significant blockage. This was confirmed with a nuclear stress test showing lateral ischemia, and the subject was still having low threshold angina.

Six months later, on 19 October one year after*, the subject was hospitalized and underwent elective cardiac catheterization with angioplasty. During surgery, there was successful placement of a drug-eluting stent in the proximal and mid portions of the first diagonal with excellent angiographic result and no acute complications; there was an unsuccessful attempt at crossing distal circumflex stenosis, likely due to chronic total occlusion. The stents were patent. Treatment included prasugrel. The event was reported as resolved on 20 October one year after* and the subject was discharged from the hospital on the same date.

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The subject's last dose of evolocumab prior to the event of angina pectoris was on 27 September one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the cutoff date on [redacted]. The investigator considered the event angina pectoris as not related to evolocumab.

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Subject No: [redacted]
Treatments: Parent Study: Placebo SC Q4W + Ezetimibe PO QD 10 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Cholelithiasis

Subject [redacted] was a 52-year-old white woman participating in Study 20110110 who developed cholelithiasis. The subject's medical history included hypercholesterolemia, Barrett's esophagus, gastroesophageal reflux disease, bronchitis, migraine, vulvovaginal dryness, constipation, sinusitis, arthropod bite, sulfa and erythromycin drug hypersensitivity. The subject was a non-smoker and denied alcohol use. Concomitant medications included ezetimibe, aciclovir, butalbital/acetylsalicylic acid/codeine phosphate, ipratropium, valaciclovir, estrogens conjugated, omeprazole, sucralfate, metoclopramide, and cyclobenzaprine. Previous treatment for hypercholesterolemia was not provided.

The subject was in the parent study from 09 December two years ago* to 02 March one year ago* and received the last dose of ezetimibe in the parent study on 03 February one year ago*. She was randomized to Study 20110110 on 02 March one year ago* and assigned standard of care treatment. After completing the first year of study, she received the first dose of evolocumab in Study 20110110 on 05 April [redacted].

Approximately 2 weeks later, on 23 April same year*, the subject was admitted to the hospital for cholelithiasis. Laboratory tests showed aspartate aminotransferase (AST) of 159 U/L and alanine aminotransferase (ALT) of 117 U/L, glucose of 116 mg/dL (previous ALT, AST and fasting glusoce were within normal range: 22 U/L, 20 U/L and 89 mg/dL respectively), white blood cell (WBC) count of 9.7 x 10^3/µL, red blood cell (RBC) count of 4.46 x 10^6/µL, blood urea nitrogen of 7 mg/dL, creatinine 0.5 mg/dL, bilirubin of 0.7 mg/dL, alkaline phosphatase of 126 U/L, and troponin I of 0.00 ng/mL. A gall bladder ultrasound showed cholelithiasis; intraoperative cholangiogram was unremarkable. Cholecystectomy was performed. Additional treatment included hydrocodone and paracetamol, ibuprofen, lidocaine, morphine, ondansetron, pantoprazole, atorvastatin, and a drug reported as "Fiorinal (acetylsalicylic acid, butalbital, caffeine, phenacetin)".

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On 24 April same year*, repeated laboratory tests showed WBC count of 6.0 x 10^3/µL, RBC count of 3.94 x 10^6/µL, glucose of 119 mg/dL, blood urea nitrogen of 6 mg/dL, creatinine of 0.6 mg/dL, AST of 121 U/L, ALT of 166 U/L, lipase of 29 U/L, bilirubin of 0.4 mg/dL, and alkaline phosphatase of 106 U/L. The next day, on 24 April same year*, the subject was discharged from the hospital. The event of cholelithiasis was reported to have resolved on 24 April same year*.

The subject's last dose of evolocumab prior to the event was on 05 April same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted].

The investigator reported that there was no reasonable possibility that the event of cholelithiasis was related to evolocumab.

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Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Diabetes mellitus, Pancreatitis

Subject [redacted] was a 71-year-old black man participating in Study 20110110 who developed diabetes mellitus (reported term: worsening of diabetes mellitus) and pancreatitis. The subject's medical history included hypercholesterolemia, and type 2 diabetes mellitus (uncontrolled). Concomitant medications included insulin aspart and glargine, glimepiride, lisinopril, terazosin, and combination of hydrochlorothiazide and losartan. Previous and current treatment for hypercholesterolemia included simvastatin.

On 27 October one year ago*, fasting glucose was 159 mg/dL and glycosylated hemoglobin was 7.9%.

The subject was in the parent study from 03 November one year ago* to 26 January same year* and received the last dose of evolocumab in the parent study on 29 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 26 January [redacted].

On the same day, the subject's glucose was 249 mg/dL. The subject was counseled. Approximately 3 months later, on 18 April same year*, laboratory tests at the week-12 visit revealed a fasting glucose level of 914 mg/dL and glycosylated hemoglobin of 15.9%. On 23 April same year*, the subject was hospitalized. Laboratory tests on the same day revealed a fasting blood glucose of 482 mg/dL and the subject was diagnosed with pancreatitis. During hospitalization, the subject was placed on a clear liquid diet. Treatment medications included insulin detemir, insulin aspart, and intravenous normal saline for dehydration. On 26 April same year*, the event of diabetes mellitus was reported to have resolved and the subject was discharged from the hospital on the same day. The event of pancreatitis was reported to have resolved on 05 May same year*. The investigator reported that the dehydration and hyperglycemia were symptoms of the pancreatitis.

The subject's last dose of evolocumab prior to the events was on 18 April same year*. The subject discontinued evolocumab due to worsening of diabetes at that time.

The investigator reported that there was no reasonable possibility that the events of diabetes mellitus or pancreatitis were related to evolocumab.

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Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Standard of care Years 2 to 5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Pulmonary embolism, Acute renal failure

Subject [redacted] was a 75-year-old white man participating in Study 20110110 who experienced pulmonary embolism (reported term: bilateral pulmonary emboli) and acute renal failure (reported term: acute on chronic renal failure). The subject's medical history included hypercholesterolemia, dyspnea, hyperkalemia, increased prostate specific antigen, edema, back pain, atherosclerosis, constipation, benign prostatic hyperplasia (BPH), syncope, essential hypertension, peripheral neuropathy, osteoarthritis, obesity (body mass index 38.92 kg/m^2), myocardial infarction, nephrolithiasis, chronic renal failure, hyperlipidemia, transurethral prostatectomy, coronary artery disease, angioplasty with cardiac stent, bilateral stenosis, cystoscopy, ureteroscopy, hydrocele operation, coronary artery arteriosclerosis, chronic obstructive pulmonary disease, interstitial lung disease, orthopedic procedure, renal artery stenosis, former tobacco user, occasional drinker, and a family history of hypertension. Concomitant medications included Vitamin E, metoprolol, amlodipine, acetylsalicylic acid, celecoxib, ubidecarenone, cyclobenzaprine, hydrochlorothiazide, hydrocodone with paracetamol, gabapentin, docusate, and azithromycin. Previous treatment for hypercholesterolemia was not known; current treatment included ezetimibe.

The subject was in the parent study from 27 December one year ago* to 19 March same year* and received the last dose of evolocumab in the parent study on 20 February same year*. The subject was randomized to the standard of care arm of Study 20110110 on 19 March [redacted].

On 07 September same year*, the subject presented to the hospital with shortness of breath, progressively getting worse over the past week; symptoms included dyspnea, exercise intolerance, lightheadedness, weakness, cough, and wheezing. A computerized tomogram (CT) performed as an outpatient demonstrated bilateral pulmonary emboli. On admission, international normalized ratio (INR) level was 1.05 and prothrombin time was 13.5. The subject's temperature was 97.8°F, pulse 71 beats per minute (bpm), respiratory rate 18 breaths/minute, oxygen saturation 91%, and blood pressure 140/70 mmHg. On the same day, a bilateral lower extremity ultrasound venous Doppler showed no sonographic evidence for deep vein thrombosis involving the right or left lower extremity. An electrocardiogram (ECG)

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showed normal sinus rhythm, low voltage QRS and inferior infarct, age undetermined. Laboratory tests revealed a white blood cell (WBC) count of 8.2 x10^3/µL, hemoglobin (Hgb) 14.5 g/dL, platelets 189 x 10^3/µL, blood urea nitrogen (BUN) 25 mg/dL, creatinine 1.49 mg/dL, and glucose 116 mg/dL. Cardiac enzymes were negative; aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and bilirubin were within normal limits. On 08 September same year* a transthoracic echocardiography revealed an estimated left ventricular ejection fraction of 60 to 65%, no focal wall motion abnormality was seen, left ventricle was normal in size with mild concentric left ventricular hypertrophy, no intracardiac masses, thrombi or shunts were seen, and diastolic dysfunction was suggested by pulse wave Doppler. The subject remained stable throughout the course of hospitalization and was started on therapeutic enoxaparin and warfarin. Additional treatment for the event included esomeprazole, sodium chloride, paracetamol, ipratropium bromide with salbutamol, cyclobenzaprine, labetalol, ondansetron, and tramadol. Upon discharge on 09 September same year*, the subject was in a stable condition and obtained an ambulatory oxygen saturation which was between 92 and 91%. The event of pulmonary embolism was reported to as resolved on 13 September same year*. The investigator stated that subject had no known history of hereditary hypercoagulable states; and clarified that subject had not undertaken lengthy air travel recently.

On 18 October same year*, the subject presented to the emergency room after a pre-syncopal episode in the shower. On admission, the subject stated that he had been experiencing intermittent falls and intermittent altered mental status.

The subject was admitted to the hospital due to acute renal failure superimposed on chronic kidney disease stage 2 to 3 and peripheral edema of uncertain etiology. Blood tests results showed glucose level of 116 mg/dL, WBC 12.6 x10^3/µL, red blood cell (RBC) count 4.4 x 10^6/µL, Hgb 13.7 g/dL, hematocrit 39.7%, platelet count 224 x 10^3/µL, neutrophils 85%, lymphocytes 7%, prothrombin time 31.2 sec, INR 3.18, activated partial thromboplastin time (APTT) 61.6 sec, sodium 137 mmol/L, potassium 4.7 mmol/L, BUN 60.0 mg/dL, creatinine 4.53 mg/dL, glomerular filtration rate (GFR) 13 mL/min/1.73m^2, calcium 9.5 mg/dL, albumin 3.7 g/dL, troponin I less than 0.1 ng/mL and sedimentation rate 86 mm/hr. The subject's fractional excretion of sodium (FENA) was 2.8%, which ruled out pre-renal azotemia. The subject's creatinine was 4.5 mg/dL. A urinalysis was positive for WBCs and RBCs, which initially suggested nephrolithiasis. At baseline on 27 December one year ago*, creatinine was 1.3 mg/dl and urinalysis was positive for RBCs. Upon admission, the subject was also noted to be slightly confused, and he had a CT of the head that showed moderate atrophy and small vessel ischemic change; mildly dilated ventricles

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likely compensatory from the degree of atrophy. Renal ultrasound showed kidneys were normal in size and echogenicity; with right renal length of 12.8 cm and left renal length of 11.9 cm; evaluation of the left kidney was very limited; no gross hydronephrosis; limited evaluation of the bladder; urinary bladder volume 251 cc. Serial troponins were monitored in order to rule out acute coronary syndrome and they all returned negative. He was also monitored on telemetry and no acute ischemic changes were noted.

On 19 October same year*, the subject stated that he had typical dribbling and weak urine stream with 2 voiding episodes daily (consistent with BPH) and reported that the previous week he had some mild back pain and thought he might be getting a kidney stone; the subject stated that he took some pain medication, and his pain resolved. Blood tests revealed INR of 2.82, glucose of 94 mg/dL, potassium of 4.2 mmol/L, sodium 135 mmol/L, BUN 56 mg/dL, creatinine 4.40 mg/dL and serial troponins were less than 0.10 ng/mL; the site reported that FENA was 2.88% signifying intrinsic renal failure. Differential diagnosis included medication induced vs hypotension induced vs post obstruction nephropathy with BPH. Gabapentin and hydrochlorothiazide were put on hold. Lower extremity edema was multifactorial. Urine culture showed Enterococcus species growth, sensitive to ampicillin, penicillin, levofloxacin, and nitrofurantoin.

On 20 October same year*, an abdominal-pelvic renal ultrasound was done and showed moderately obstructing stone just below the right ureteropelvic junction measuring 1.2 cm; right renal stones; exophytic lesion along the lateral surface of the kidney measuring 1.2 cm could represent hemorrhagic cyst; severe hydronephrosis of the left kidney with multiple stones and a 7 mm stone in the proximal left ureter; and circumferential wall thickening of the rectum. That day, the subject underwent cystoscopy with bilateral ureteral stent placement and fluoroscopy without complications. Operative findings included bilateral hydronephrosis and cloudy urine obtained from the right collecting system; a brisk drip of relatively clear urine from the upper collecting system was seen. Following this procedure, the subject had significant improvement in his creatinine level to 1.4 mg/dL. As gabapentin was held, it was noted that subject had gradual improvement in his mental status. The change in mental status was attributed to gabapentin, as the subject's wife correlated the change in mental status with the initiation of gabapentin. Warfarin was held briefly for ureteral stent placement and was resumed post-procedure.

At discharge, on 23 October same year*, the subject's creatinine level was 1.45 mg/dL, glucose 96 mg/dL, phosphorus 4.1 mg/dL, potassium 4.4 mmol/L, sodium 141 mmol/L, BUN 25 mg/dL,

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GFR 47 mL/min, INR 1.55, Hgb 13.6 g/dL, platelet count 281 x 10^3/µL, RBC 4.4 x 10^6/µL and WBC of 8.1 x 10^3/µL. Treatment medications included piperacillin/tazobactam, renal electrolytes, sodium chloride, unspecified intravenous solutions, ondansetron, cefazolin, ampicillin, morphine, hydrocodone, azithromycin, enoxaparin, docusate, brompheniramine/paracetamol/phenylephrine, paracetamol, oxycodone/paracetamol, labetalol, bisacodyl, and macrogol. The event of acute renal failure was reported as resolved on 23 October same year* and the subject was discharged from the hospital on the same day.

After completing 1 year in the study, the subject received the first dose of evolocumab on 16 April one year after*. As of the data cutoff date of [redacted], the subject was continuing in the study, and the last dose of evolocumab prior to the cutoff date was on [redacted].

The investigator reported that there was no reasonable possibility that the events of pulmonary embolism and acute renal failure were related to any study activity.

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Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 420 mg Year 1 treatment: Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Encephalopathy, Cervical radiculopathy, Tension headache

Subject [redacted] was a 65-year-old white woman participating in Study 20110110 who developed tension headache, cervical radiculopathy (reported term: right-sided cervical radiculopathy) and encephalopathy. The subject's medical history included back pain, glaucoma, hiatal hernia, hysterectomy, lumbar laminectomy with cervical fusion, cervical radiculopathy, large intestine polyp and irritable bowel syndrome. Concomitant medications included conjugated estrogens, ranitidine, zolpidem tartrate, Vitamin D, loratadine, prednisone and acetylsalicylic acid. Previous treatment for hypercholesterolemia was not reported and ongoing treatment for hypercholesterolemia included omega-3 fish oil.

The subject was in the parent study from 18 October one year ago* to 09 January same year* and received the last dose of evolocumab in the parent study on 15 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 11 January [redacted].

Approximately one year later, on 25 March two years after*, the subject experienced neck pain and was seen at an urgent care. The subject was started on prednisone and hydromorphone for the pain. Later, the subject became quite lethargic and was not able to walk. The subject's family interrupted the medication. On an unknown date in March two years after*, the subject developed altered mental status which was considered to be due to rapid steroid taper and high dose of narcotics. The subject also experienced severe pain and weakness in her right arm due to cervical radiculopathy. On 26 March two years after*, the subject was hospitalized due to encephalopathy, right sided cervical radiculopathy and tension headaches. The subject's vital signs were normal. No significant laboratory abnormalities were found. Head computed tomography scan and chest radiograph were unremarkable. Impression of the subject's condition included altered mental status secondary to use of narcotic medication, cervical radiculopathy, dehydration, and steroid withdrawal. The subject was started on fluids including sodium chloride, morphine, and laxative. The subject was discharged from the hospital on 03 April two years after*. The event of encephalopathy was considered resolved on 11 April two years after* and tension headache and cervical radiculopathy

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were ongoing at the time of this report. The subject's last dose of evolocumab prior to the event was on 10 March two years after. Evolocumab was temporarily withheld.

As of the data cutoff date of [redacted], the subject was continuing in the study, and the last dose of evolocumab prior to the cutoff date was on [redacted].

The investigator reported that there was not a reasonable possibility that the events of encephalopathy, cervical radiculopathy, and tension headache were related to the investigational product.

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Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Esophageal spasm, Depression (multiple events), Anxiety, Suicidal ideation (multiple events), Diabetic ketoacidosis

Subject [redacted] was a 64-year-old white woman participating in Study 20110110 who experienced esophageal spasm, depression (multiple events) (reported term: worsening depression), anxiety, diabetic ketoacidosis, and suicidal ideation (multiple events). The subject's medical history included hypercholesterolemia and hyperlipidemia, obesity, drug hypersensitivity (to codeine, tamoxifen and penicillin), depression, bipolar disorder, self inflicted injury, suicidal ideation (with previous psychiatric inpatient treatment), restless legs syndrome, urinary incontinence, peripheral arterial occlusive disease, hypertension, spinal osteoarthritischronic sinusitis, diverticulosis, arteriosclerosis, cerebrovascular disease, insomnia, astigmatism, gastroesophageal reflux disease, chronic diarrhea, type 2 diabetes mellitus, and hypothyroidism. The subject was an ex-smoker, currently consumed alcohol, and had a family history of depression, suicide, and alcohol addiction. Concomitant medications included glyceryl trinitrate, cyanocobalamin, quetiapine, aripiprazole, metformin, ascorbic acid, colecalciferol, pioglitazone, olmesartan, eszopiclone, nefazodone, lorazepam, lurasidone, mirtazapine, lisinopril, temazepam, azelastine, combination of cetirizine and pseudoephedrine, combination of fexofenadine and pseudoephedrine, combination of amoxicillin and clavulinic acid, acetylsalicylic acid, iron, Vitamin B complex, iron, lamotrigine, methylphenidate, combination of bacillus coagulans and calcium carbonate, liothyronine, omega-3 fatty acids, venlafaxine, lithium, clonazepam, alprazolam, losartan, ceftriaxone, paracetamol, levofloxacin, olanzapine, hydrocodone, fluconazole, ciprofloxacin, insulin, bupropion, triamcinolone, and glimepiride. Previous treatment for hypercholesterolemia included simvastatin, ezetimibe, fenofibrate, rosuvastatin, omega-3-acid ethyl ester, and nicotinic acid.

The subject was in the parent study from 25 October one year ago* to 17 January same year* and received the last dose of evolocumab in the parent study on 20 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 17 January [redacted]. Approximately 10 months later, on 28 November same year*, the subject was hospitalized due to esophageal spasm with acid reflux and unspecified chest pain. She presented with a 3-week history of sharp, piercing,

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intermittent chest pain with acute onset of chest pressure radiating across her chest. Troponin I was 0.01 ng/mL, creatine kinase muscle-bone (MB) 2.5 µg/L and glycosylated hemoglobin was 7.5%. Electrocardiogram (ECG) was normal. Chest radiograph showed no acute cardiopulmonary process. Stress test and an echocardiogram were normal. Myocardial infarction was ruled out by serial cardiac enzymes and serial ECGs. Treatment included omeprazole for 6 weeks, and the subject was recommended to avoid reflux-related foods. The event of esophageal spam resolved on 29 November same year*, and the subject was discharged on the same date.

The last dose of evolocumab prior to the onset of the event of esophageal spasm was on 20 November same year*. Evolocumab was continued. The investigator reported that there was not a reasonable possibility that the event of esophageal spasm was related to evolocumab.

The subject was under psychiatric counseling once a week and had worsening of depression on 05 December same year*. Approximately 1 year after the first dose of evolocumab in Study 20110110, on 02 January one year after*, the subject voluntarily presented to the emergency department with worsening of depression and was hospitalized. The subject had suicidal intentions and for the last 2 weeks she had been self inflicting injuries. On admission, extensive cuts were noted on her abdomen, breasts, lower abdomen, and her back. Additionally, the subject had a low-grade fever and urinary tract infection. Urinalysis was grossly infected with positive nitrites, 1+ leukocyte, 100 to 150 WBCs, and 4+ bacteria. Urine culture results revealed >100,000 col/mL *Klebsiella pneumonia*. Treatment included ceftriaxone sodium intravenously for the infection, and lithium, lamotrigine, quetiapine, venlafaxine, and olanzapine for the psychiatric condition. Additional medication included levofloxacin. On 09 January one year after*, mental status examination showed spontaneous speech, linear thought process, good mood, and euthymic affect. She denied any suicidal thoughts. The event of depression was considered resolved on 08 January one year after*, and the subject was discharged from hospital on 09 January one year after*.

The subject's last dose of evolocumab prior to the event of depression (onset on 02 January one year after*) was on 19 December same year*. Evolocumab was continued. The investigator reported that there was not a reasonable possibility that the event of depression (05 December same year*) was related to evolocumab. No suspect medication was reported.

Approximately 1 year after the first dose of evolocumab in Study 20110110, on 24 January one year after*, the subject was again hospitalized due to worsening of depression, anxiety and self-inflicted

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lesions. The assessment revealed major depressive syndrome, noted as; probable borderline personality disorder; stressors were unknown at that time. The subject was continued on venlafaxine. Upon psychiatric examination, the subject was found to have excessive daytime sleepiness, insomnia, snoring and a Mallampati score of 4, all consistent with sleep disorder breathing. The subject was continued on metformin and venlafaxine, and lisinopril and olmesartan medoxomil were also administered. Repeated laboratory test showed the troponin I of < 0.04 ng/mL. A cardiology consultation confirmed that the subject had no active coronary ischemia that was of concern, and there were no cardiac contraindications to electroconvulsive therapy (ECT). On 04 February one year after*, the subject started her course of ECT. Treatment medications included lurasidone, venlafaxine, and mirtazapine. She improved after 1 ECT, and was transitioned to outpatient ECT. On 05 February one year after*, the subject was discharged from the hospital. The events of depression (onset on 24 January one year after*) and anxiety were reported resolved on 05 February one year after*.

The subject's last dose of evolocumab prior to the events of depression and anxiety was on 15 January one year after*. Evolocumab was continued. The investigator reported that there was not a reasonable possibility that the events of depression and anxiety were related to evolocumab.

Approximately 1 year and 4 months after the first dose of evolocumab in Study 20110110, on 29 May one year after*, the subject again experienced worsening depression associated with suicidal ideation and was electively hospitalized. The subject had been undergoing ECT, which had been ineffective, and she had been cutting herself again. Upon admission, a mental status examination revealed suicidal thoughts. Since the subject reported ill reactions to monoamine oxidase inhibitors (MAOIs) in the past, treatment included lithium. On 04 June one year after*, laboratory tests revealed a lithium level of 0.9 mmol/L. On 05 June one year after*, glucose levels were 106 to 146 mg/dL. On 07 June one year after*, the subject reported doing much better and denied any suicidal thoughts. Mental status examination revealed good mood with affect good and appropriate to mood. The events of depression (onset on 29 May one year after*) and suicidal ideation were reported as resolved on 07 June one year after*, and the subject was discharged on the same date with plans for starting a partial hospitalization program and continuing on lithium, lurasidone, mirtazapine, clonazepam, and venlafaxine.

The subject's last dose of evolocumab prior to the events of depression (onset on 29 May one year after*) and suicidal ideation was on 16 May one year after*. Evolocumab was continued. The investigator

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reported that there was not a reasonable possibility that the events of depression (onset on 29 May one year after*) and suicidal ideation were related to the evolocumab. No medications were considered co-suspect.

The subject experienced worsening of depression and diabetic ketoacidosis on 21 November one year after* and was hospitalized. Bupropion was initiated to treat depression on 21 November one year after*. The depression resolved on 22 November one year after* and was not considered related to evolocumab. The subject received insulin lispro and magnesium in the hospital to treat ketoacidosis that also resolved on 22 November one year after* and was not considered related to evolocumab.

The subject's last dose of evolocumab prior to the event of depression was on 29 October one year after* and evolocumab was continued.

The subject experienced suicidal ideation on 02 December one year after*, was hospitalized and was treated with alprazolam and olanzapine. The event resolved on 14 December one year after* and was not considered related to evolocumab.

As of the data cutoff date [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff date on [redacted].

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Evolocumab SC Q2W 140 MG Year 1 Treatment: Standard of Care Years 2-5 treatment: Evolocumab SC Q4W 140 mg + Standard of care
Report: Ulna fracture

Subject [redacted] was a 67-year-old Asian woman participating in Study 20110110 who experienced an ulna fracture (reported term: open fracture of olecranon [left]). The subject's medical history included dyslipidemia, osteoporosis, and worsening of coronary artery disease. Concomitant medications included acetylsalicylic acid, minodronic acid, and combination medicine of liver oil, gelatin, glycerin, and modified starch; collagen, diphenhydramine salicylate, diprophylline, betahistine and nutritional supplement. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin.

The subject participated in the parent study from 10 July one year ago* to 16 October one year ago* and received the last dose of evolocumab in the parent study on 18 September one year ago*. The subject was randomized to standard of care on 16 April [redacted].

On 22 January one year after*, the subject was injured in a car accident and was taken to the emergency department. The subject experienced neck pain and contusion (reported term: lumbar bruise). She was diagnosed with open fracture of olecranon (left) and was hospitalized on the same day. On 23 January one year after*, corrective surgery was performed. Treatment reported after the onset of the event included rocuronium, sugammadex, fentanyl, propofol, cefazolin, and paracetamol. The outcome of the events was reported as ongoing. The subject was discharged on 01 February one year after*.

As of the data cutoff date of [redacted], the subject was continuing in the study.

The investigator reported that there was not a reasonable possibility that the event open fracture of olecranon (left) was related to the study participation.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: AMG 145 SC Q4W 420 mg Year 1 treatment: Standard of care
Report: Inguinal hernia

Subject [redacted] was a 54-year-old Asian man participating in Study 20110110 who developed an inguinal hernia. The subject's medical history included hypercholesterolemia. Concomitant medication included Vitamin E. Previous and ongoing treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 21 August one year ago* to 13 November one year ago* and received the last dose of evolocumab in the parent study on 16 October one year ago*.

The subject was randomized to Study 20110110 on 12 March [redacted] and assigned standard of care treatment. The subject did not receive evolocumab. Approximately 6 months after the subject was randomized, on 04 September same year*, the subject developed inguinal hernia. The subject was hospitalized on 18 October same year* and underwent a laparoscopic percutaneous extraperitoneal closure the same day. There were no relevant results of laboratory, imaging or consultations during the hospitalization. Treatment included sennoside A+B, zolpidem tartrate, combination of cyanocobalamin, pyridoxine hydrochloride, and thiamine hydrochloride; ascorbic acid, carbazochrome sodium sulfonate, cefazolin, propofol, remifentanil hydrochloride, ephedrine hydrochloride, combination of calcium gluconate monohydrate, glucose, magnesium chloride hexahydrate, potassium chloride, sodium acetate, sodium chloride, and sodium citrate dihydrate and ropivacaine hydrochloride. The event of inguinal hernia was reported as resolved on 21 October same year*. The subject was discharged from the hospital on 24 October same year*.

As of the data cutoff date of [redacted], the subject was continuing in the study. The investigator reported that there was no reasonable possibility that the event of inguinal hernia was related to study conduct. There were no co-suspect medications.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study and regimen: Placebo SC Q2W Year 1 Treatment: Evolocumab SC Q4W 420 mg + SOC Years 2-5 treatment: Evolocumab + Standard of care
Report: Feces discolored

Subject [redacted] was a 76-year-old Asian man participating in Study 20110110. The subject experienced feces discoloration (reported term: black stool). The subject's medical history included hypercholesterolemia and sleep apnea. Previous and ongoing treatment for hypercholesterolemia included pitavastatin. Concomitant medications included amlodipine, azilsartan, ubidecarenone, combination of acetylsalicylic acid, aluminum glycinate, and magnesium carbonate.

The subject participated in the parent study from 11 September one year ago* to 18 December one year ago* and received the last dose of placebo in the parent study on 20 November one year ago*. The subject received the first dose of evolocumab in the Study 20110110 on 07 May [redacted].

The subject experienced an event of black stool and was sent to the hospital on suspicion of gastrointestinal hemorrhages on 30 November same year* and was hospitalized on the same day. The subject underwent gastroscopy on 30 November same year* which revealed gastrointestinal reflux disease (GERD). Laboratory tests were performed on 03 December same year* revealed hematocrit of 28.4%, hemoglobin of 9.1 g/dL, and red blood cell count of 272 $x10^4$ µL. The subject underwent colonoscopy on 04 December same year* which revealed diverticulum of colon. The event remained unresolved; however, the subject was discharged on 05 December same year*. Treatment medications after the onset of the event included lansoprazole.

On 10 December same year*, the subject underwent gastroscopy and colonoscopy which did not diagnose gastrointestinal hemorrhages. The event was reported to have resolved on 10 December same year* since gastrointestinal hemorrhages were not recognized.

The subject's last dose of evolocumab prior to the event was on 19 November same year*. As of the data cutoff date of [redacted] the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted].

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event black stool was related to evolocumab.

Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Unstable angina

Subject [redacted] was a 68-year-old Asian man participating in Study 20110110 who developed unstable angina. The subject's medical history included hypercholesterolemia, angina since 06 September six years ago*, mild chronic kidney failure and heartburn since April same year*. She was a former smoker. Concomitant medications included acetylsalicylic acid, lansoprazole, and allopurinol. Previous and current treatment for the condition under study included pravastatin.

The subject was in the parent study from 27 December one year ago* to 21 March same year* and received the last dose of evolocumab in the parent study on 21 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 21 March [redacted].

Approximately 8 months later, on 21 November same year*, the subject developed unstable angina. A positron emission tomography revealed advanced myocardial ischemia of the anteroseptal apex; electrocardiogram (ECG) revealed sinus bradycardia and ST elevation consistent with epicardial injury, pericarditis, or early repolarization. Treatment reported after the onset of the event included adenosine triphosphate disodium hydrate and dimethicone.

On 26 November same year*, the subject was admitted to the hospital and cardiac catheterization was performed. The procedure revealed stenosis of 50% on targets 2 and 6 and 99% to 100% on target 7. Angioplasty was performed on target 7, and subsequent intravascular ultrasound evaluation revealed good flow. ECGs were performed immediately after the procedure and 2 hours later. The first ECG showed sinus bradycardia; abnormal Q wave on III and aVF; negative T on V3; and ST-T segment abnormality on I, aVL, V2, V4, and V5. The second ECG showed sinus bradycardia; negative T on V3; and ST-T segment abnormality on I, aVL, V2, V4, and V5. Additional treatment during the event included fosfomycin and clopidogrel. On 27 November same year*, the event resolved and the subject was discharged.

The last dose of evolocumab prior to the event was on 31 October same year*. Evolocumab was continued.

*新薬承認情報提供時に置き換え

The investigator stated that there was not a reasonable possibility that the event unstable angina was related to evolocumab.

As of the data cutoff date of [redacted] the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted].

Subject No: [redacted]
Treatment: Parent study: Evolocumab SC Q4W 280 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Malignant lung neoplasm (multiple events)

Subject [redacted] was a 71-year-old Asian man participating in Study 20110110 who was diagnosed with malignant lung neoplasm (reported term: lung carcinoma). The subject's medical history included hypercholesterolemia, benign prostatic hyperplasia, cervical myelopathy, type 2 diabetes mellitus, diabetic neuropathy, duodenal ulcer, hepatic steatosis, cholelithiasis, previous smoking and squamous cell carcinoma of right lung from 11 November nine years ago* to 07 November two years ago*, treated with chemotherapy and radiotherapy Concomitant medications included candesartan cilexetil, and vildagliptin. Previous and current treatment for hypercholesterolemia included rosuvastatin.

No relevant baseline laboratory tests results were reported.

The subject was in the parent study from 07 January same year* to 01 April same year* and received the last dose of evolocumab in the parent study on 04 March same year*. The subject received the first dose of evolocumab in Study 20110110 on 15 April [redacted].

On 25 November same year*, chest radiograph and computerized tomogram (CT) scans revealed massive right pleural effusion and mediastinal lymph node swelling, suspicious for lung carcinoma. Pleural effusion cytology revealed class V and suspected recurrent squamous cell carcinoma of the lung. On the same day, relevant laboratory tests disclosed carcinoembryonic antigen (CEA) 17.1 µg/L and , cytokeratin fragment antigen (CYFRA) 3.5 ng/mL. On 26 November same year*, sputum cytology was class II.

Six days later, on 02 December same year* during the week-32 visit, the subject had hemoptysis more than 10 times per day with dyspnea. Additional laboratory tests disclosed CEA 45.7 µg/L, neuron-specific enolase (NSE) electrochemiluminescence immunoassay (ECLIA) 25.9 ng/mL, and progastrin-releasing peptide (pro-GRP) 6580.4 pg/mL. The subject was diagnosed with lung carcinoma. Treatment reported after the onset of the event included carbazochrome sodium sulfonate, tranexamic acid, and ambroxol hydrochloride. Evolocumab was temporarily

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withheld. Two days later, on 04 December same year*, the subject was admitted to the hospital for further examination and treatment.

Thoracic drainage was performed by using aspiration catheter from 05 December same year* to 10 December same year*. On 06 December same year*, contrast enhanced CT diagnosed pleural dissemination and multiple pulmonary metastases. On 10 December same year*, an abdomen echography found liver metastasis, gallbladder stone, and left renal cyst. Considering results of the second pleural effusion cytology, pro-GRP 6580 pg/mL, and CEA 1577 µg/L, it was diagnosed as small cell carcinoma. Pleurodesis was performed using cisplatin. On 13 December same year*, the aspiration catheter was removed.

Additional treatment reported after the onset of the event included loxoprofen, iohexol, granisetron, cefotiam, cefcapene pivoxil, dexamethasone, lenograstim, cefepime, chlordiazepoxide, enterococcus faecalis tablets, etoposide, pethidine, lansoprazole, cisplatin, aprepitant, furosemide, irinotecan, paracetamol, ketoprofen, oxetacaine, flurbiprofen, tramadol, hyoscine butylbromide, and lecicarbon suppositories.

On 02 March one year after*, the subject completed 3 cycles of chemotherapy and was discharged from the hospital temporarily. On 11 March one year after*, the subject was readmitted for additional chemotherapy. The event of malignant lung neoplasm was considered as resolved on 04 April one year after*.

The subject's last dose of evolocumab prior to the event was on 28 October same year*. The decision was taken to discontinue evolocumab on 04 December same year* and the last dose of evolocumab was on 28 October same year*. As of the data cutoff date of [redacted], the subject was continuing in the study.

The investigator reported that there was not a reasonable possibility that the event lung carcinoma was related to evolocumab. No co-suspect medications were identified by the investigator.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study: Placebo SC Q2W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Cortical cataract

Subject [redacted] was a 69-year-old Asian woman participating in Study 20110110 who developed a cortical cataract (reported term: cortical cataract, right). Her medical history included ovarian cystoma, gastric polyps reflux esophagitis, and previous cortical cataract in the left eye. Concomitant medications included acetylsalicylic acid, clopidogrel, metoprolol, and rabeprazole. Previous and current treatment for the condition under study was not reported.

The subject was in the parent study from 28 November one year ago* to 08 March same year* and received placebo. The subject received the first dose of evolocumab in Study 20110110 on 23 April [redacted].

Approximately 10 months and 2 weeks later on 11 March one year after*, the subject was seen by her ophthalmologist and was diagnosed with right cortical cataract. Approximately 2 months later on 15 May one year after*, the subject was hospitalized. On 16 May one year after* the subject underwent surgery which included phacoemulsification, aspiration, and intraocular lens implant. The subject was discharged on 16 May one year after*. The outcome of the event cataract cortical (right) was reported as resolved on 02 June one year after*. The subject's last dose of investigational product prior to the event was on 24 April one year after*. Evolocumab was continued

The subject's last dose of evolocumab prior to event was not known. As of the data cutoff date of [redacted], the subject was continuing in the study and received her last dose of evolocumab on [redacted].

The investigator reported that there was not a reasonable possibility that the event was related to evolocumab or to the study procedures.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study and regimen: Evolocumab SC Q2W 70 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab + Standard of care
Report: Sudden hearing loss

Subject [redacted] was an 80-year-old Asian woman participating in Study 20110110 who developed sudden hearing loss (reported term: sudden deafness [left ear]). The subject had a history of hypercholesterolemia. The subject's medical history also included constipation, a large intestinal polyp, hemorrhoids, hyperuricaemia, a fracture of the right femur shaft, back pain, insomnia, high levels of C-reactive protein, hypertension, osteoporosis, contusion of right forearm, rotator cuff tendinitis of the right shoulder, and dermatitis contact. Concomitant medications included diltiazem, etizolam, methyldopa, sennoside A and B, sofalcone, alendronate sodium, etodolac, rebamipide, ketoprofen, posterisan and diclofenac. Previous and ongoing treatment for hypercholesterolemia included pravastatin.

The subject was in the parent study from 06 December one year ago* to 14 March same year* and received the last dose of evolocumab in the parent study on 14 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 23 May [redacted].

Approximately 8 months later on 26 January one year after*, the subject developed dizziness and hearing impairment. On 27 January one year after*, the subject called for an ambulance and was transferred to a hospital with an otolaryngology department. The treatment medications after the onset of the event included omeprazole, adenosine triphosphate, difenidol, mecobalamin, and hydrocortisone. The subject was discharged from the hospital on 07 February one year after*. The outcome of the event sudden hearing loss was reported as unknown.

The subject's last dose of evolocumab prior to hospitalization was on 26 December same year*. As of the data cutoff date of [redacted] the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted].

The investigator reported that there was not a reasonable possibility that the event sudden deafness (left ear) was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q2W 140 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Diabetes mellitus

Subject [redacted] was a 59-year-old Asian woman participating in Study 20110110 who developed diabetes mellitus (reported term: worsening of diabetes mellitus). The subject's medical history included hypercholesterolemia and diabetes mellitus since eight years ago*. Concomitant medications included acetylsalicylic acid; combination of azelnidipine and olmesartan; esomeprazole, flurbiprofen, pitavastatin, ketoconazole, and hydrocortisone butyrate. Previous and current treatment for hypercholesterolemia included pitavastatin.

The subject was in the parent study from 18 September one year ago* to 25 December one year ago* and received the last dose of evolocumab in the parent study on 27 November one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 07 May [redacted].

Laboratory tests performed on the same day (07 May same year*) revealed glucose level of 10.8 mmol/L and glycosylated hemoglobin of 9.2% (fasting glucose at randomization was 9.27 mmol/L). Approximately 1 month later, on 04 June same year*, repeated laboratory tests showed glucose level of 11.7 mmol/L and glycosylated hemoglobin of 9.2%. The subject was hospitalized on 01 July same year* due to worsening of diabetes mellitus. The subject did not have any interruption/non-compliance in diabetic treatment, dietary changes, or any intercurrent illness or infection. During hospitalization, on 10 July same year*, the subject's glucose level was 7.8 mmol/L. Treatment medication included metformin. On 12 July same year*, the subject received nutritional guidance and her blood sugar control improved with diet therapy and treatment medication. The event of diabetes mellitus was reported as resolving and the subject was discharged from the hospital on 13 July same year*. The subject was prescribed sitagliptin and voglibose at discharge and was advised to continue metformin.

The subject's last dose of evolocumab prior to the event was on 04 June same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff date on [redacted].

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The investigator reported that there was not a reasonable possibility that the event of diabetes mellitus was related to evolocumab. The event was considered to be related to a change in the subject's lifestyle.

Subject No: [redacted]
Treatment: Parent Study: Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Appendicitis

Subject [redacted] was a 34-year-old Asian man participating in Study 20110110 who developed appendicitis (reported term: acute appendicitis). The subject's medical history included hypercholesterolemia, hepatic steatosis, chronic cardiac failure, and congestive cardiomyopathy. Concomitant medications included indapamide, spironolactone, digoxin, enalapril, carvedilol, voglibose, tenelgliptin hydrobromide, montelukast, seretide, theophylline, and Kakkonto (traditional Japanese herbal medicine). (Although diabetes and asthma were not reported in the medical history, the subject received medications to treat diabetes and asthma; discussion is ongoing with the study site to clarify). Previous treatment for hypercholesterolemia was not reported; ongoing treatment included pitavastatin.

The subject was in the parent study from 21 December one year ago* to 15 March same year* and received the last dose of placebo in the parent study on 15 February same year*. The subject received the first dose of evolocumab in Study 20110110 on 24 May [redacted].

Approximately 1 month and 1 week later, on 02 July same year*, the subject experienced nausea and vomiting and was monitored for suspected acute gastroenteritis. On 05 July same year*, the subject underwent a computerized tomogram that suggested acute appendicitis and peritonitis. He was hospitalized for conservative therapy. On the same day, 05 July same year*, laboratory test results showed: C-reactive protein 1.12 mg/dL, lymphocyte count 20.0%, neutrophil count 70.2%, red blood cell (RBC) count 5.55 x 10^6/µL, and white blood cell (WBC) count 14.5 x 10^9/µL. Repeated laboratory tests on 09 July same year* revealed C-reactive protein 0.62 mg/dL, lymphocyte percentage 30.4%, neutrophil percentage 58.9%, RBC count 4.81 x 10^6/µL, and WBC count 9.4 x 10^9/µL. Treatment included cefmetazole, levofloxacin, and oxapium iodide. The subject was discharged from the hospital on 10 July same year*. The event of appendicitis was reported to have resolved on 19 July same year*.

The subject's last dose of evolocumab prior to the event was on 21 June same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and the last dose of evolocumab prior to the cutoff date was on [redacted].

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The investigator reported that there was no reasonable possibility that the event of appendicitis was related to evolocumab.

Subject No: [redacted]
Treatments: Parent study: Evolocumab SC Q4W 420 mg Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care (SOC) Years 2-5 treatment: Evolocumab SC Q4W 420 mg + SOC
Report: Abnormal electrocardiogram ST segment, Coronary artery occlusion

Subject [redacted] was a 74-year-old Asian man participating in Study 20110110 who had an abnormal electrocardiogram (ECG) ST segment (reported term: ST change) and coronary artery occlusion (reported term: left circumflex coronary artery occlusion). The subject's medical history included hypercholesterolemia, coronary artery bypass graft, dyslipidemia, diabetes mellitus, angina pectoris, chronic cardiac failure; he was an ex-tobacco user. Concomitant medications included warfarin, rabeprazole, voglibose, isosorbide mononitrate, benzbromarone, furosemide, glimepiride, acetylsalicylic acid, and felbinac. Previous and current treatment for hypercholesterolemia included rosuvastatin.

The subject was in the parent study from 24 January same year* to 18 April same year* and received the last dose of evolocumab in the parent study on 21 March same year*. The subject received his first dose of evolocumab in Study 20110110 on 23 May [redacted].

Approximately 1 month later, on 20 June same year*, an ECG showed an ST change; there were no subjective symptoms. Laboratory test results on this day were white blood cell count 8.4 x 10^3/µL, red blood cell count 5.10 x 10^6/µL, hemoglobin 16.0 g/dL, hematocrit 46.7%, platelet count 17.7 x 10^4/µL, neutrophil count 3.91 x 10^3/µL, albumin 4.2 g/dL, total protein 7.0 g/dL, urea 21.1 mg/dL, creatinine 0.82 mg/dL, sodium 138.7 mEq/L, potassium 4.2 mEq/L, chloride 105.3 mEq/L, brain natriuretic peptide 31.6 pg/mL, glomerular filtration rate 69.8 mL/min, and blood creatine phosphokinase 123 IU/L.

On a stress ECG on 20 June same year* findings were ST abnormalities in leads I, II, V3-V6, but the test was considered negative. Heart rate remained 65 to 78 bpm. The subject was hospitalized on 27 June same year*. An ultrasound echocardiogram showed left ventricular (LV) motion: the region inferior to the base I-S appeared somewhat hypoechoic; the base through the middle of the posterior was high echo, but the systolic thickening was maintained; ejection fraction was 53% in M-mode, more than 60% apparently. Results were negative for left ventricular hypertrophy (LVH), enlargement of left ventricular end-diastolic dimension (LVDd), and

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right-sided enlargement. Coronary angiography on 28 June same year* showed left anterior descending artery (LAD) (segment) #7 90%, left circumflex artery (LCx) #11 90%; right coronary artery (RCA) #1 100%, UTA-LAD #7 patent, aorta-saphenous vein graft (AO-SVG)-LCx #12 occluded, AO-SVG-LCx #3 patent, left internal thoracic artery (LITA)-LAD # 7 patent. The LCx lesion did not require revascularization or further follow-up. Treatment included lidocaine, povidone-iodine, cefotiam, and levofloxacin. The subject was discharged from the hospital on 29 June same year*.

As of the data cutoff date of [redacted], the events of abnormal ECG ST segment and coronary artery occlusion remained unresolved.

The subject's last dose of evolocumab prior to the events was on 20 June same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study and received the last dose of evolocumab prior to the data cutoff on [redacted].

The investigator reported that there was not a reasonable possibility that the events of abnormal ECG ST segment and coronary artery occlusion were related to evolocumab. No medications were considered co-suspect.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Placebo SC Q2W Year 1 treatment: Standard of Care
Report: Uterine prolapse

Subject [redacted] was a 59-year-old Asian woman participating in Study 20110110 who experienced uterine prolapse. The subject's medical history included hyperlipidemia, hypertension and angina pectoris. Concomitant medications included acetylsalicylic acid, furosemide, loxoprofen, Vitamin E, and losartan. Previous and ongoing treatment for hypercholesterolemia included pravastatin.

The subject was in the parent study from 05 September one year ago* to 12 December one year ago* and received the last dose of placebo in the parent study on 14 November one year ago*. The subject was randomized to Study 20110110 on 15 May [redacted] and assigned standard of care treatment. The subject did not receive evolocumab. Approximately 2 months later, on 15 July same year*, the subject experienced a strange feeling at the genital area and visited the gynecologist, and uterine prolapse was diagnosed. Approximately 2 months later, on 12 September same year*, the subject was admitted to the hospital and a hysterectomy was performed on 13 September same year*. The investigator reported that the subject did well after the operation. No further information was provided. The event of uterine prolapse was reported to have resolved on 23 September same year* and the subject was discharged from the hospital on the same day.

As of the data cutoff date of [redacted], the subject was continuing in the study. The investigator reported that there was no reasonable possibility that the event of uterine prolapse was related to any study activity or procedure.

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Subject No: [redacted]
Treatments: Parent Study: Study 20110231, Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Contusion, Scapula fracture, Pubis fracture

Subject [redacted] was a 76-year-old Asian man participating in study 20110110 who experienced a contusion (reported term: bruise of head), scapula fracture (reported term: fracture of right coracoids of scapula), and pubis fracture (reported term: fracture of right pubis and ischium). The subject's medical history included hypercholesterolemia, hyperlipidemia, hypertension, insomnia, headache, and osteoporosis. Concomitant medications included nifedipine, bisoprolol, brotizolam, calcium L-aspartate hydrate, alfacalcidol, tocopherol acetate, Vitamin E, silodosin, loxoprofen sodium hydrate, ketoprofen, betamethasone butyrate propionate, paraffin liquid/polyethylene resin and ketoconazole. Previous and ongoing treatment for hypercholesterolemia included pravastatin.

The subject was in the parent study from 05 October one year ago* to 26 December one year ago* and received the last dose of placebo in the parent study on 28 November one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 11 April [redacted].

Approximately 4 months later, on 11 August same year*, the subject was found lying at the foot of the stairs and had a contusion, scapula fracture, pubis fracture, and fractured ischium. He was hospitalized and had clear sensorium, but had lost his memory at the time of the accident. He had right shoulder, lower back, and right hip joint pain. Later on the same day, the subject had a head computerized tomography (CT) which showed no obvious bleeding. The chest and abdominal CT scans showed a fracture of the right pubis and ischium. The radiograph showed compression fracture of the third lumbar vertebra (possibly obsolete) and a fracture of the right coracoids of scapula.

On 12 August same year*, the head CT showed no traumatic change. On 14 August same year*, magnetic resonance imaging of the lumbar vertebrae showed compression fracture of the third lumbar vertebra was diagnosed as obsolete. The subject was hospitalized for 4 weeks for bed rest. Evolocumab was withheld. The investigator reported brotizolam as a co-suspect medication.

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On 02 September same year*, the subject started gait training. On 11 September same year*, the subject was transferred to another facility for rehabilitation.

The subject was discharged from the hospital on 13 October same year*. At this time, the subject was able to walk and his outpatient rehabilitation continued twice a week. The outcome of the events of fracture of right coracoids of scapula, fracture of right pubis and ischium was reported as resolving.

The subject's last dose of evolocumab prior to the event was on 01 August same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted]. The investigator reported that there was no reasonable possibility that the events of contusion, fracture of right coracoids of scapula, and fracture of right pubis and ischium were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Placebo SC Q4W Year 1 treatment: Evolocumab SC Q2W 420 mg + Standard of care Years 2-5 treatment: Evolocumab SC Q4W 420 mg + Standard of care
Report: Gastric cancer

Subject [redacted] was a 62-year-old Asian man participating in Study 20110110 who was diagnosed with gastric cancer (reported term: advanced gastric cancer). His medical history included hypercholesterolemia, chronic sinusitis, sinus operation due to chronic sinusitis, intervertebral disc protrusion, diabetes mellitus, hyperlipidemia, hepatic steatosis, and tobacco use. He had a family history of gastric cancer. Concomitant medications included voglibose, sitagliptin, glimepiride, lansoprazole, nateglinide, Daiichi-Sankyo Icyouyaku (a drug for functional gastrointestinal disorder), chondroitin sulfate, propolis, dimeticone, iopamidol, glimepiride, pethidine HCl, sennoside A & B, ephedrine, flurbiprofen, expafusin, cefazolin, solita-T1, parenteral nutrition solutions, neurobion, hydroxyzine, diclofenac, pentazocine, loxoprofen, rebamipide, gimeracil with oteracil and tegafur, aprepitant, cisplatin, mannitol, dexamethasone, furosemide, granisetron, aprepitant, dextramethasone, neurobion, metoclopramide, flucose, iopamidol, and lenograstim. Previous and current treatment for hypercholesterolemia included pitavastatin.

The subject was in the parent study from 02 February same year* to 27 April same year* and received the last dose of placebo in the parent study on 30 March same year*. The subject received the first dose of evolocumab in Study 20110110 on 27 April [redacted].

Approximately 6 months later, on 12 October same year*, the subject underwent gastroscopy which was suspicious for scirrhous gastric cancer. At that time, the administration of investigational product was held due to results of the gastroscopy (the subject's last dose of evolocumab was on 14 September same year*). Histopathology revealed signet ring cell carcinoma, group 5 and the subject was diagnosed with advance gastric cancer. Laboratory tests revealed alpha 1 fetoprotein (AFP) of 2.5 ng/mL, carbohydrate antigen 19-9 (CA 19-9) 12.8 µ/mL and carcinoembryonic antigen (CEA) of 6.5 ng/mL. On 19 October same year*, a contrast enhanced computed tomography revealed fatty liver and no metastasis. On 23 October same year*, a colonoscopy revealed colon polyp and internal hemorrhoids.

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On 05 November same year*, the subject was hospitalized and an abdominal ultrasonography showed a fatty liver. Subsequently, on 07 November same year* the subject underwent a planned gastrectomy. New liver metastasis and para-aortic lymph node metastasis were not observed in the abdominal cavity. Cancer infiltrated circumferentially from the gastric body to pylorus. Treatment included concomitant medication lansoprazole. On 22 November same year*, a pathology test revealed advanced gastric cancer (stage III) with positive lymph node metastases (8/11). The subject was discharged later that same day.

On 05 December same year*, the subject was re-admitted to the hospital and a surgery was performed for a blood access port on the right chest. On 06 December same year*, anticancer therapy with cisplatin was started and the subject was discharged from the hospital on the same day.

On 15 March one year after*, an abdominal ultrasonography was performed and the subject was diagnosed with a hepatic metastasis of an advanced gastric cancer. The subject's gastric cancer stage was upgraded from III into IV.

On 19 March one year after*, the subject's contrast enhanced CT showed peritoneal dissemination and the metastases of para-aortic lymph nodes. Also, the investigator commented that chemotherapy was terminated because the radical treatment was difficult in this condition.

At the time of the last available report, the event was not resolved.

The subject's last dose of evolocumab prior to the event and in the study was on 14 September same year*. Evolocumab was permanently discontinued due to the event, gastric cancer. As of the data cutoff date of [redacted], the subject was continuing in the study.

The investigator reported that there was not a reasonable possibility that the event gastric cancer was related to the investigational product.

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Subject No: [redacted]
Treatments: Parent Study: Evolocumab SC Q2W 70 mg Year 1 treatment: Standard of care
Report: Unstable angina; Angina pectoris

Subject [redacted] was a 75-year-old Asian man participating in Study 20110110 who developed unstable angina (reported term: unstable angina requiring hospitalization) and angina pectoris (reported term: effort angina). The subject's medical history included hypercholesterolemia, intervertebral disc degeneration, cholelithiasis, angina pectoris, hypertension; and he had undergone a coronary artery bypass graft. Concomitant medications included Vitamin E, magnesium oxide, acetylsalicylic acid, ranitidine, diltiazem, and flurbiprofen. Previous and ongoing treatment for hypercholesterolemia included pravastatin.

The subject participated in the parent study, Study 20110231, from 10 October one year ago* to 18 January same year* and received the last dose of evolocumab in the parent study on 19 December one year ago*. The subject was randomized to Study 20110110 on 28 May [redacted] and assigned standard of care treatment.

Approximately 2 months and 2 weeks after randomization, on 10 August same year*, the subject experienced chest discomfort, which resolved without any medication. On 19 August same year*, the subject was hospitalized due to chest discomfort. On admission, the subject received glyceryl trinitrate and symptoms were relieved. An electrocardiogram (ECG) showed significant ST depression at I, aVL, V 4-6 (suspected myocardial damage), sinus rhythm, stenosis of left coronary artery, and abnormal T wave (suspected anterolateral myocardial ischemia). Laboratory test results showed creatine phosphokinase (CPK) of 66 IU/L and 74 IU/L, creatine phosphokinase muscle-brain (CK-MB) of 11 IU/L and 9 IU/L, troponin T of 0.007 ng/mL, C-reactive protein of 0.05 mg/dL, potassium of 4.0 mEq/L, and sodium of 140 mEq/L. Laminagraphy showed left ventricular end-systolic diameter (LVDs): 49.0 mm; LVDs: 25.5 mm; ejection fraction: 79%;

On 20 August same year*, an ECG revealed ST elevation at II, III, and aVF, and CPK was 54 IU/L. A laminagraphy showed left ventricular end-diastolic dimension (LVDd): 44 mm; LVDs: 30.6 mm; ejection fraction: 59.1%. Electrocardiogram revealed sinus rhythm, significant ST depression (more than 0.1 mV ST depression aVL, V2, V3, V4), inferior myocardial damage, significant ST elevation (II, aVF). The subject had multiple ECGs done on the same day and was diagnosed

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with an acute myocardial infarction. The same day, coronary angiography revealed a stenosis of 99% in segment 2 of the right coronary artery. A percutaneous coronary intervention was performed and a drug eluting stent was placed; the stenosis improved from 99% to 0%. Coronary angiography revealed another stenosis at segment 12 of the left circumflex artery.

On 21 August same year*, CPK level was 120 IU/L, and an ECG revealed sinus rhythm, medium degree of ST depression, abnormal T wave (suspected lateral myocardial ischemia), and slight left axis deviation. Subsequent ECG revealed sinus rhythm, non-specific T wave abnormality, and slight left axis deviation. The CPK level was 97 IU/L on 22 August same year* and 42 IU/L on 24 August same year*. The CPK level was 36 IU/L on 29 August 2013.

On 30 August same year*, the subject underwent a percutaneous coronary intervention for the lesion at segment 12 of the left circumflex artery. A drug eluting stent was placed and the stenosis improved from 90% to 0%. Treatment included clopidogrel, heparin, nicorandil, isosorbide dinitrate, and atropine. Additionally, the subject received hydroxyzine, mepivacaine, pentazocine, cefazolin, potassium aspartate, iomeprol, magnesium sulfate, povidine-iodine, and sodium nitroprusside hydrate. The event of unstable angina was reported as resolved on 02 September same year*, and the subject was discharged from the hospital on the same day. The investigator confirmed that hypertension was a predisposing risk factor associated with the event and the subject did not have a history of previous episodes of unstable angina.

The investigator reported that there was not a reasonable possibility that the event of unstable angina was related to any study activity or procedure.

Again, on 24 March one year after*, the subject developed effort angina and was hospitalized for restudy. Coronary angiography was conducted, which showed progression of a stenosis in segment 3 of the right coronary artery from 75% to 90%. A drug-eluting stent was placed and stenosis improved from 90% to 0%. The subject's ECG was normal. The ejection fraction was 69.8 %, left ventricular (LV) wall hypertrophy and chamber dilation was found to be negative. Treatment medications reported after the onset of event included hydroxyzine, lidocaine, ioxilan, mepivacaine, heparin, isosorbide, nitroprusside, nicorandil, atropine, noradrenaline, and cefazolin. The outcome of the event effort angina was reported as resolved on 26 March one year after* and the subject was discharged from the hospital on the same day. The subject was recommended for follow-up examination by angiography.

As of the data cutoff date of [redacted], the subject was continuing in the study with standard of care treatment.

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The investigator reported that there was not a reasonable possibility that the event angina pectoris was related to the study conduct.

Subject No: [redacted]
Treatment: Parent study and regimen: Placebo SC Q4W Year 1 treatment: Evolocumab SC Q4W 420 mg + Standard of care Years 2-5 treatment: Evolocumab + Standard of care
Report: Tendon rupture

Subject [redacted] was a 61-year-old Asian man participating in Study 20110110 who experienced a tendon rupture (reported term: biceps brachii tendon rupture [left arm]). The subject had a history of hypercholesterolemia, hypertension, asthma, and seasonal allergy. Concomitant medications included amlodipine, allopurinol, montelukast sodium, and telmisartan. Previous and ongoing treatment for hypercholesterolemia included pravastatin.

The subject was in the parent study from 27 October one year ago* to 18 January same year* and received the last dose of evolocumab in the parent study on 21 December one year ago*. The subject received the first dose of evolocumab in Study 20110110 on 11 May [redacted].

Approximately 5 months later, on 16 October same year*, the subject injured his left arm while lifting a heavy object, which led to a biceps brachii tendon rupture. On 28 October same year* the subject underwent biceps tenodesis surgery. Treatment medications after the onset of the event included sennoside AB calcium, flurbiprophen axetil, metoclopramide, neomycin, cefazolin and cefcapene. The event was reported as resolving. The subject was transferred to another hospital on 01 November same year*. The investigator reported that the subject recuperated at home after discharge. The event was reported as resolved on 18 December same year*.

The subject's last dose of evolocumab prior to hospitalization was on 28 September same year*. As of the data cutoff date of [redacted] the subject was continuing in the study, and received the last dose of evolocumab prior to the data cutoff date on [redacted].

The investigator reported that there was not a reasonable possibility that the event biceps brachii tendon rupture (left arm) was related to evolocumab.

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